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Organo-transition-metal chemistry of highly fluorinated ligand systems

IX *. Chemical and biological aspects of novel organo-transition-metal hexafluoro-arsenates and -antimonates

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Abstract

The reaction of Cp_2MCl_2 (M = Ti, V) with two equivalents of $AgEF_6$ (E = As, Sb) in SO_2 led to the quantitative preparation of the hexafluoropnicogenate complexes $Cp_2Ti(AsF_6)_2$, $Cp_2Ti(SbF_6)_2$ and $Cp_2V(SbF_6)_2$. $Cp_2Ti(Sb_2F_{11})_2$ was prepared from $Cp_2Ti(SbF_6)_2$ and stoichiometric amounts of SbF_5. By reaction of $Cp_2Ti(AsF_6)_2$ with the neutral Lewis base CH_3CN the cationic metallocene derivatives $[Cp_2Ti(CH_3CN)_n]^{2+}$ $[AsF_6^-]_2$ ($n = 2, 3$) could be obtained. The relatively high stability of these covalent and cationic titanocene hexafluoroarsenates toward water is of great interest because of their biological activity. The germicidal activity of a number of metallocene hexafluoropnicogenate complexes has been investigated. Although neither the "Cp_2Ti^{2+}" unit nor AsF_6^- show a strong bactericide activity, the metallocene perfluoropnicogenate species do show this effect. A possible reaction mechanism is discussed.

Introduction

The reaction of metallocene dichlorides with nitriles in the presence of suitable Lewis acids yields ionic complexes with nitrile ligand bonded to the transition metal M [3–6]. Recently we succeeded in the synthesis of the first stable Lewis base free $Cp_2M(EF_6)_2$ ($Cp = \eta^5\text{-}C_5H_5$; M = Ti, V; E = pnicogen) complexes where the EF_6 unit is directly coordinated to the Cp_2M fragment [7,8]. These species can be prepared quantitatively from Cp_2MCl_2 (M = Ti, V) and $AgEF_6$ (E = As, Sb) (eq. 1)

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* For VIIIth communication see ref. 1. This paper was presented as a poster at the ESIC IV [2].

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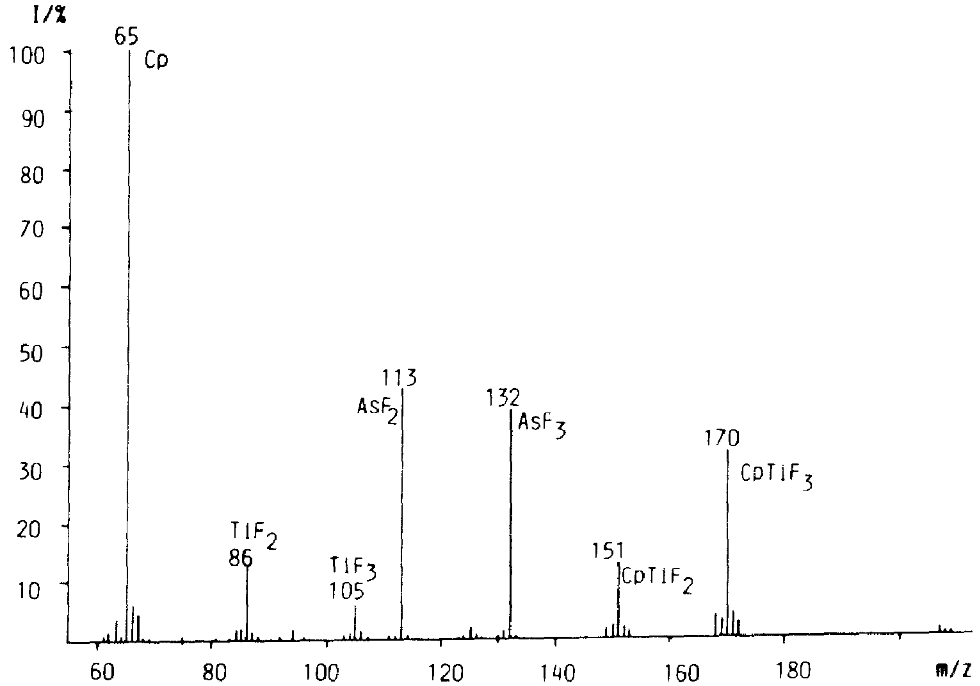

Fig. 1. Mass spectrum (EI, 70 eV, 60° C) of $Cp_2Ti(AsF_6)_2$.

or by reaction of Cp_2TiF_2 with AsF_5 or SbF_5 (eq. 2) and were characterized by chemical analysis, IR, mass, NMR and X-ray spectroscopy [7,8].

$$Cp_2MCl_2 + 2\ AgEF_6 \xrightarrow{SO_2} Cp_2M(EF_6)_2 + 2\ AgCl \qquad (1)$$

$$Cp_2TiF_2 + 2\ EF_5 \xrightarrow{SO_2} Cp_2Ti(EF_6)_2 \qquad (2)$$

The stability of $Cp_2Ti(AsF_6)_2$ compared with $Cp_2Ti(PF_6)_2$ which does not exist in the solid state [9] can be explained by the higher F^- affinity of AsF_5 (464 kJ/mol) compared with PF_5 (422 kJ/mol) [10,11]. From thermodynamic estimates [12] it can be concluded that $Cp_2Ti(AsF_6)_2$ is thermodynamically unstable with respect to decomposition reactions involving F transfer to the transition metal according to eq. 3.

$$(\pi\text{-}Cp)_2TiCl_2 + AsF_5 \rightarrow (\pi\text{-}Cp)TiCl_2F + \text{“}(\sigma\text{-}Cp)AsF_4\text{”} \qquad (3)$$

However, $Cp_2Ti(AsF_6)_2$ is kinetically stabilized and exists in solution and in the solid state. The mass spectrum does not show a peak due to the molecular ion but one corresponding to $CpTiF_3$.The isotopic pattern of this peak corresponds to the ion $CpTiF_3^+$ rather than to the ion AsF_5^+. This indicated that a F transfer from the AsF_6 group to the transition metal occurs as a decomposition at low temperature. This is in agreement with the As^V–F and Ti^{IV}–F bond energies (As–F: 406, Ti–F: 584 kJ/mol) (Fig. 1) [8].

As the ^1H NMR spectroscopy was not sufficient to elucidate the Cp_2Ti–AsF_6 bond situation in solution, we also investigated this problem by temperature-dependent ^{19}F NMR spectroscopy. In addition to this it seemed to be of interest whether the stable $Cp_2Ti(AsF_6)_2$ would react with neutral ligands, yielding cationic titanocene derivatives.

Since the metallocene hexafluoro-arsenates and -antimonates can be prepared from Cp_2MF_2 and EF_5 we were interested to achieve a simple synthesis of Cp_2MF_2. One possible way, the reaction of Cp_2MCl_3 with ClF (eq. 4), was estimated to be thermodynamically favoured by 144 kJ/mol [13].

$$Cp_2TiCl_2 + 2\ ClF \rightarrow Cp_2TiF_2 + 2\ Cl_2 \qquad (4)$$

Metallocene derivatives of the early transition elements often show biological activity and Ti and V complexes have been tested for their antiproliferative activity [14–18].Especially polar and hydrophilic ionic species are of interest in terms of their higher solubility in water-like solvents [19]. The solubility and the stability in water of some of the hexafluoropnicogenate complexes have been analysed. These observations led to our interest in the microbiological activity. We were especially interested in the germicidal activity of these complexes since discovery of the elongation of *Escherichia coli* was the first hint to the biological activity of inorganic Pt complexes (*cis*-platin) [20–22] which led to the detection of pronounced antitumor effectivity [23,24].

In this contribution we report the synthesis, characterization and reaction behaviour of the As and Sb containing hexafluoro complexes mentioned above as well as preliminary results of their biological activity.

Reaction of Cp_2TiCl_2 with ClF

By the reaction of Cp_2TiCl_2 with ClF neither Cp_2TiClF nor Cp_2TiF_2 but only $CpTiCl_3$ (with traces of $CpTiCl_2F$) was identified as the product (^1H NMR and mass spectroscopy) [13]. Nevertheless the reaction according to eq. 4 should be exothermic by −144 kJ/mol [13]. However, a reaction according to eq. 5 was estimated to be even more thermodynamically favourable, ΔH −358 kJ/mol [13].

$$Cp_2TiCl_2 + ClF \rightarrow CpTiCl_3 + \text{“CpF”} \qquad (5)$$

So one can easily understand why a process in agreement with eq. 5 and not that as indicated in eq. 4 occurs. Moreover, the sums of the bond energies of Ti–Cl (429 kJ/mol) and C–F (485 kJ/mol) on one side and Ti–F (585 kJ/mol) and C–Cl (327 kJ/mol) on the other side explain, that $CpTiCl_3$ is formed as the main product and only a small amount of $CpTiCl_2F$ was found [13].

Reaction of $Cp_2Ti(AsF_6)_2$ with neutral Lewis base molecules

The reaction of $Cp_2Ti(AsF_6)_2$ with an excess of CH_3CN led in 100% yield to the preparation of the cationic complex molecule $[Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2$ according to eq. 6 [13]. One of the three CH_3CN ligands can be removed by pumping on the ionic compound at higher temperature according to eq. 7 [13].

$$Cp_2Ti(AsF_6)_2 + 3\ CH_3CN \rightarrow [Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2 \qquad (6)$$

$$[Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2 \xrightarrow[-CH_3CN]{40-50\,^\circ C} [Cp_2Ti(CH_3CN)_2]^{2+}[AsF_6^-]_2 \qquad (7)$$

The integration of the proton NMR spectrum of $[Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2$ in SO_2 solution clearly shows the composition of the complex to be the 1/3 adduct.

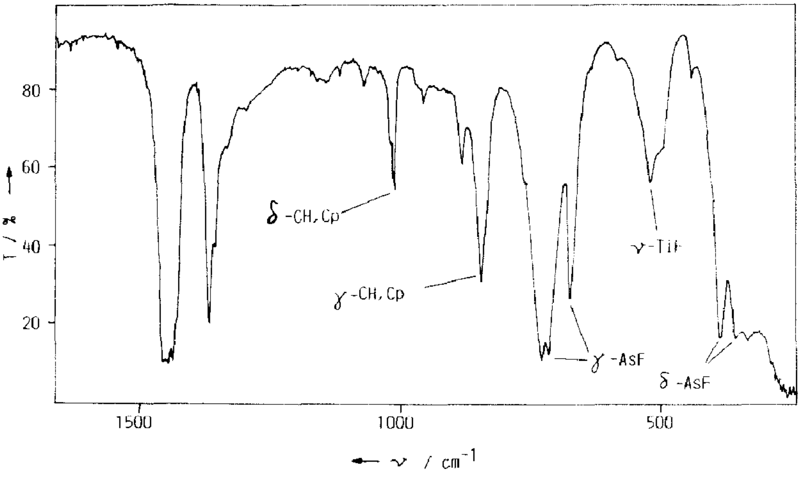

Fig. 2. Infrared spectrum of $Cp_2Ti(AsF_6)_2$ in Nujol.

Also in SO_2 solution the CH_3CN is still coordinated as the only methyl singlet appears at 2.67 ppm, whereas free acetonitrile in SO_2 has a chemical shift of 2.05 ppm [13]. It is interesting that a species with three CH_3CN ligands, which corresponds to a Ti with 36 electrons was observed. One CH_3CN is lost to generate the more familiar 34 electron species, which is less crowded and more stable but coordinatively unsaturated.

Because of the much lower basicity of CF_3CN compared with CH_3CN, $Cp_2Ti(AsF_6)_2$ does not react with an excess of CF_3CN, yielding a cationic complex in analogy to the observed reaction with CH_3CN. Moreover, no reaction could be observed with carbon monoxide, either when applied as a gas or in SO_2 solution. Assuming that the crystal lattice energies of the CH_3CN and the CF_3CN adduct are more or less identical, the energy gain due to the coordination of CF_3CN to Cp_2Ti^{2+} is less than the sum of the energy terms due to the entropy and Ti $\cdots$ AsF_6-bond

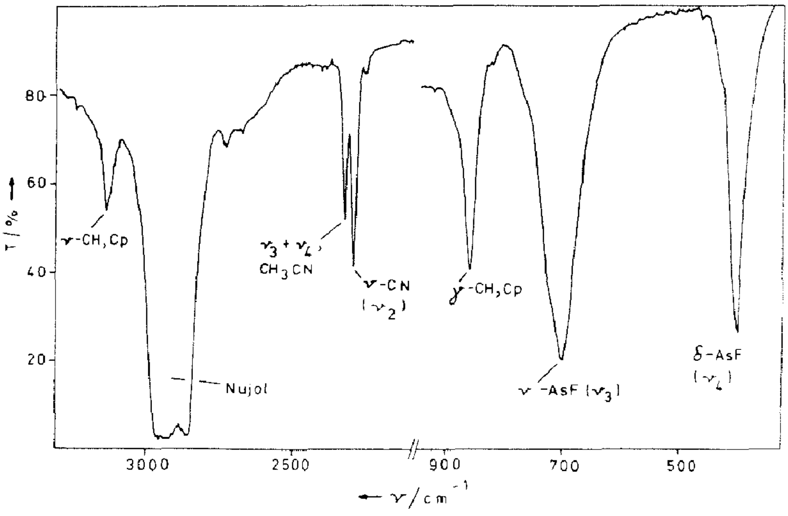

Fig. 3. Infrared spectrum of $[Cp_2Ti(CH_3CN)_3]^{2+}$ $[AsF_6^-]_2$ [13].

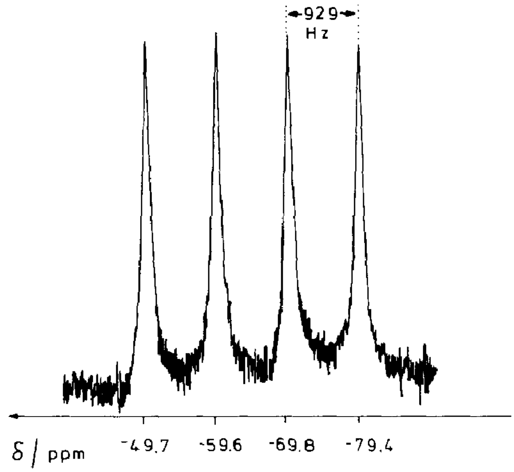

Fig. 4. ^{19}F NMR spectrum of $[Cp_2Ti(CH_3CN)_3]^{2+}$ $[AsF_6^-]_2$ at −40 °C in CD_3CN [25].

interaction, which are working against the salt formation. In the solid state of $[Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2$ there is no direct bonding between the metallocene cation and the AsF_6^- anion which was observed in $Cp_2Ti(AsF_6)_2$ by X-ray crystallography and IR spectroscopy [8]. A strong and broad absorption in the IR spectrum of $Cp_2Ti(AsF_6)_2$ at 530 cm^{-1} was assigned to the Ti–F symmetric and

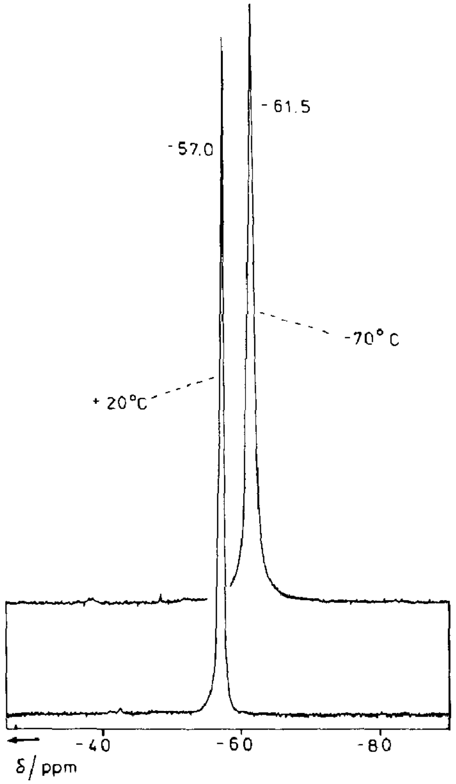

Fig. 5. ^{19}F NMR spectrum of $Cp_2Ti(AsF_6)_2$ at +20 °C and −70 °C in SO_2.

asymmetric stretching mode (Fig. 2) [8]. The disappearance of this band in the IR spectrum of $[Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2$ (Fig. 3) [13] indicates that there is no direct bonding between the metallocene cation and the AsF_6^- anion. Free acetonitrile shows the CN stretching mode (ν_2) at 2254 cm^{-1}. In the discussed complex this band is shifted to 2293 cm^{-1}. This result indicates that the cationic titanocene complex has strong σ-donor ($CH_3CN \rightarrow Ti$) bonding (N.B. due to the low basicity this is not possible for CF_3CN).

The ^{19}F NMR spectrum of the cationic complex in CD_3CN and also in SO_2 even at low temperature (−40 °C) consists of a nicely resolved four line pattern due to the As–F coupling (I, $^{75}_{33}As = 3/2$) in the octahedral AsF_6^- anion (Fig. 4) [14]. On the other hand, $Cp_2Ti(AsF_6)_2$ dissolved in SO_2 shows at room temperature in the ^{19}F NMR spectrum only one peak which does not split into the expected pattern even at low temperature (−70 °C) (Fig. 5). This indicates free highly symmetric AsF_6^- ions in the ionic complex, whereas the AsF_6 group is coordinated to the Ti centre in $Cp_2Ti(AsF_6)_2$, showing rapid exchange (pseudorotation) even at low temperature. Apparently the pseudorotation of coordinated AsF_6 is fast enough that all F appear equivalent but slow enough that no As–F coupling is observed.

Stability of $Cp_2Ti(AsF_6)_2$ and $[Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2$ toward water

The reactivity of the neutral and the ionic $[Cp_2Ti(CH_3CN)_3]^{2+}[AsF_6^-]_2$ toward water (D_2O) has been investigated and elucidated by proton and ^{19}F NMR spectroscopy [25]. Both compounds dissociate into ionic pairs. Due to the pH value ($pH < 3.5$, saturated solution) the titanocene group (Cp_2Ti) remains intact. Also the AsF_6^- anion seems to be stable at the low pH value, after a small amount (14–20%, relating to F) has hydrolysed yielding DF, which was identified by ^{19}F NMR spectroscopy.

Microbiological aspects

Whereas neither Cp_2TiCl_2 (or its hydrolysis products) nor $KAsF_6$ show strong antimicrobiological activity, the perfluoropnicogenate complexes $Cp_2Ti(AsF_6)_2$, $Cp_2V(SbF_6)_2$ and $Cp_2Ti(Sb_2F_{11})_2$ have a minimal inhibition concentration (MIC) equal or similar to the MIC observed for hydrofluoric acid (Tab. 1) [1].

These results can be explained by a destabilization of the EF_6^- ion when it is coordinated to the metallocene fragment and both hydrolysis products, HF and

Table 1

MIC values for some perfluoropnicogenate compounds and related species. Bacteria: *E. coli*. T 32 °C; t 72 h

Complex	MIC ($g \cdot g^{-1}$)
Cp_2TiCl_2	$\gg 10^{-2}$
$Cp_2Ti(AsF_6)_2$	10^{-3}
$Cp_2Ti(Sb_2F_{11})_2$	10^{-2}
$Cp_2(SbF_6)_2$	10^{-2}
HF	10^{-3}
$KAsF_6$	$\gg 10^{-2}$

"H_3EO_4", possess strong bactericidal activity. The lower MIC values for the As derivatives compared with the Sb complexes can be explained by the generally lower toxicity of inorganic Sb^V compounds compared with As^V species [26]. It is very likely that the first step of hydrolysis of $Cp_2M(EF_6)_2$ (M = Ti, V; E = As, Sb) is the formation of $Cp_2M(EF_6)F$ and EF_5OH^- as otherwise (EF_6^- and $Cp_2M(EF_6)OH$) the decomposition should stop at the hydrolysis products of $Cp_2M(OH)(OH_2)^+$ and EF_6^- without a significant bactericidal activity.

After five weeks it was noticed that under the treatment of $Cp_2Ti(AsF_6)_2$ the bacteria became elongated to approximately four times the length of the reference sample. Surprisingly the anti-tumor agent Cp_2TiCl_2 did not show this effect and *E. coli* may behave differently when treated with an titanocene complex than with *cis*-platinum.

Conclusion

Recently we reported the synthesis of $Cp_2Ti(EF_6)_2$ (E = As, Sb), which was the first example of a titanocene complex containing MF_6^- groups directly coordinated to the metallocene centre and opened up the organometallic chemistry of highly fluorinated inorganic ligand systems of the early transition elements. The present paper summarises our last communications dealing with some chemical and biological aspects of the new organo transition metal hexafluoro-arsenates and -antimonates.

The thermodynamic values (fluoride ion affinities) encouraged us to make the (successful) synthesis of the novel hexafluoropnicogenate compounds. Further (thermodynamically) well planned experiments should afford numerous new fluorine containing organometallic compounds. By the convenient route of salt elimination, species like $Cp_2M(EF_6)_2$ (M = Ti, V; E = As, Sb) have been prepared and characterized. The reaction of $Cp_2Ti(AsF_6)_2$ with the neutral Lewis base CH_3CN led to the preparation of a new cationic metallocene derivative. This result shows the possibility to use these hexafluoropnicogenate complexes as intermediates in preparative organometallic chemistry.

The relatively high stability of these covalent and cationic titanocene hexafluoroarsenates toward water is of great interest because titanocene and especially ionic titanocene derivatives are of interest in terms of their antiproliferative activity. The microbiological activity of a number of metallocene hexafluoropnicogenate complexes has been investigated. In contrast to Cp_2TiCl_2 and $KAsF_6$ these species surprisingly show a strong germicidal activity. This effect can be explained by the appearance of biologically active products in the hydrolysis, which was followed by means of proton and fluorine NMR spectroscopy.

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